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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/698,323	10/27/2000	Jeffrey M. Isner	47624DIV(71417)	6299

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EDWARDS ANGELL PALMER & DODGE LLP
P.O. BOX 55874
BOSTON, MA 02205

EXAMINER	
KAUFMAN, CLAIRE M	

ART UNIT	PAPER NUMBER
1646	

MAIL DATE	DELIVERY MODE
02/26/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/698,323	ISNER ET AL.	
	Examiner	Art Unit	
	CLAIRE KAUFMAN	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *50,52,55-63,65-68,70,72-78 and 84* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50,52,55,56-63,65-68,70,72-78,84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to **Art Unit 1646**.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/12/09 has been entered.

Response to Amendment

The rejection under 35 USC 102(e) as anticipated by Kaplan et al. (US 5,941,868) is withdrawn in view of the amendment to the claims.

The rejection under 35 USC 102(b) as anticipated by Ferrara et al. (US 5,332,671) is withdrawn in view of the amendment to the claims.

The rejection under 35 USC 103(a) as being unpatentable over Kaplan et al. (US 5,941,868) in view of Hammond et al. (US 5,880,090) is withdrawn upon further reconsideration of the Declaration filed 2/17/2004.

The rejection under 35 U.S.C. 103(a) as being unpatentable over either Kaplan et al. (US 5,941,868; IDS submitted on 01/09/07) or Ferrara et al. (US 5,332,671) in view of Bussolino et al. (J. Clin. Invest. 87:986-995, 1991; IDS) is withdrawn in favor of the new rejections set forth below.

The rejection of claims 50, 52, 55-63, 65-68, 70, 72-78 and 84 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 5,980,887 in view of in view of Hammond et al. (U.S. Patent 5,880,090) and Asahara et al. (Science 275:964-967, 1997) is withdrawn in favor of the new rejection below relying on

Asahara et al. (1997) and Boussilino (Path. Res. Pract. 190:834-839, 1994) instead of Hammond (US 5,880,090).

Response to Amendment

Upon further consideration, the declaration of Dr. Asahara filed on 2/17/04 under 37 CFR 1.131 is sufficient to overcome the Hammond et al. US 5,880,090 reference.

Drawings

It is noted that the drawings of the instant application are informal as designated on the New Application Transmittal form filed 10/27/00.

Specification

The disclosure is objected to because of the following informalities: There are two typographical errors: p. 31, line 31, "*prior to* to", p. 34, line 24, "of We investigated".

Appropriate correction is required.

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested:

Method for inducing new blood vessels with VEGF and GM-CSF.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 50, 55-63, 65-67 and 84 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3-4 and 11 of U.S. Patent No. 5,980,887 for the reasons set forth in the previous Office Action (8/11/08; pages 18-19).

Claims 50, 55-63, 65-67 and 84 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 49-52, 54-59, 62-65 and 68-69 of the copending Application No. 10/696,391 for the reasons set forth in the previous Office Action (8/11/08; pages 22-23).

Claims 50, 55-63, 65-67 and 84 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 49, 58-60 and 68-70 of the copending Application No. 10/714,574 for the reasons set forth in the previous Office Action (8/11/08; pages 23-24).

New:

Claims 50, 52, 55-63, 65-68, 70, 72-78 and 84 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 5,980,887 in view of Boussilino (Path. Res. Pract. 190:834-839, 1994) and Asahara et al. (Science 275:964-967, Feb 1997, cited on the IDS filed 1/18/02)

An embodiment of the instant claims are directed to a method for inducing formation of new blood vessels in a mammal having chronic or acute ischemia or a method for preventing or reducing the severity of blood vessel damage in a mammal having chronic or acute ischemia comprising administering to the mammal an effective amount of a vascular endothelial growth factor (VEGF) and GM-CSF.

Claims 1-11 of U.S. Patent No. 5,980,887 are directed to a method for inducing the formation of new blood vessels in an ischemic tissue in a patient in need thereof or a method for treating an injured blood vessel in a patient in need thereof, said method (claim 2) comprising the step of administering to the patient an endothelial progenitor cell and an endothelial cell mitogen selected from the group consisting of acidic and basic fibroblast growth factors, vascular endothelial growth factor, … granulocyte/macrophage CSF and nitric oxide synthase. The treatment includes for ischemic cardiomyopathy and myocardial ischemia (claim 5). Claim 6 specifies that the endothelial cells are CD34+ or Flk-1+. US 5,980,887 does not teach administration of both VEGF and GM-CSF.

Bussolino et al. teach that (p. 835, sentence bridging col. 1-2), "Subnanomolar concentrations of GM-CSF and G-CSF induce the proliferation of endothelial cells derived from human vessels…." They also state (p. 835, col. 2, first full paragraph), "The primary effect of GM-CSF and G-CSF on vasculature *in vivo* is the stimulation of the angiogenesis process…. GM-CSF also induces angiogenesis in rat connective tissues probably by a direct effect on endothelial cells and by a recruitment and activation of macrophages which release angiogenetic factors.[57]" It is noted by the authors that (p. 836, col. 2, second full paragraph), "...*in vivo* bone marrow endothelial cells proliferate in subjects treated with GM-CSF[53]."

Asahara et al. showed CD34+ mononuclear blood cells are capable of differentiating into endothelial-like cells, and the circulating CD34+ or Flk-1+ cells may participate in the repair of ischemic tissue (p. 965). In animal models of ischemia (mouse and rabbit models of induced unilateral hindlimb ischemia), Asahara et al. also taught that syngeneic or autologous endothelial cell progenitors home in and are incorporated into capillaries and small arteries in the neovascular zones of the induced ischemic limb (see abstract and pages 965-966).

It would have been obvious to an ordinary skilled artisan to modify the claims in U.S. Patent No 5,980,887 by also administering into the patient in need of induced new blood vessels in an ischemic tissue or a patient in need of treatment for an injured blood vessel an agent such as GM-CSF to mobilize an effective level of bone marrow-derived endothelial progenitors to home into sites of active angiogenesis to repair ischemic tissues by forming new blood vessels in light of the teachings of Bussolino et al. and Asahara et al. An ordinary skilled artisan would have been motivated to carry out the above modification because Bussolino et al. already taught

that GM-CSF was capable of inducing proliferation of endothelial cells to form vessels and Asahara et al. showed endothelial cells are capable of homing in and incorporating into capillaries and small arteries in the neovascular zones of the induced ischemic limb. Therefore, the further administration of at least GM-CSF would reasonably have been expected to enhance the therapeutic effects for at least a patient in need of induction of new blood vessels in an ischemic tissue or a patient in need of treatment for an injured blood vessel. Because GM-CSF and VEGF promote angiogenesis, administration of either or both prior to the injury would have been obvious with the timing of administration determined by routine optimization. An ordinary skilled artisan would have had a reasonable expectation of success in light of the teachings 5,980,887, Bussolino et al. and Asahara et al., and coupled with a high level of skill possessed by an ordinary skilled artisan in the relevant art.

Applicants' intention of addressing the double patenting rejections upon indication of otherwise allowable subject matter is acknowledged.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 52, 68, 84 and dependent claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 52 and 84 are indefinite because they recite 'increasing frequency' of endothelial progenitor cells (EPCs). It is unclear what is meant by this. In the specification, there is a discussion of increased frequency by percent (*e.g.*, p. 6, line 12) as well as an "increase in the frequency of the circulating EPCs" (p. 34, line 29). However, there is also a discussion of enhancement of mobilization (*e.g.,* paragraph bridging pages 30-31). It is unclear if the phrase is meant to refer to an increase in the actual number of EPCs or an increase in movement of EPCs.

Claims 52 and 84 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps.

See MPEP § 2172.01. The omitted steps are: the formation of new blood vessels. The method step does not necessarily accomplish the intended use set forth in the preamble. This rejection could be obviated by adding a phrase at the end of the claims stating, for example, "thereby inducing the formation of new blood vessels."

Claim 68 is indefinite because it recites "VEGF or GM-CSF is coadministered with at least one angiogenic protein." However according to the specification (p. 20, lines 12-25), both VEGF and GM-CSF are angiogenic proteins themselves. This rejection could be obviated by adding a word such as "additional" after "at least one" in the claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 50, 53, 55-63, 65-68, 70, 72-78 and 84 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses GM-CSF, granulocyte-macrophage colony-stimulating factor, as disclosed, for example, in WO 86/00639 and an analog called LEUKINE® which is commercially available (p. 17, lines 4 and 25). These known GM-CSF proteins meet the written description provision of 35 USC 112, first paragraph. However, the claims are directed to or encompass proteins having substantial sequence identity to a published human GM-CSF (p. 17, lines 1-4) or a proteins structurally related to a natural GM-CSF which is a functional equivalent (p. 17, lines 15-20). Also disclosed is a natural GM-CSF protein with from 1-5 amino acids changes which remains a full functional equivalent. With the exception of known GM-CSF proteins and a GM-CSF proteins which differ from the wildtype with from 1-5 amino acids changes and which remain a full functional equivalent (p. 17, lines 14-19), none of the others meets the written description provision of 35 USC 112, first paragraph.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483 (BPAI 1993). In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only known GM-SCF proteins and GM-CSF proteins which differ from the wildtype with from 1-5 amino acids changes and which remain a full functional equivalent of the wildtypel protein, but not the full breadth of the claim meets the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 50, 52, 55-63, 65-68, 70, 72-78 and 84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ferrara et al. (US 5,332,671, PTO-892 mailed 1/23/08) in view of Bussolino et al. (Path. Res. Pract. 190:834-839, 1994) and Orazi et al. (Blood, 79(10):2610-2619, 1992).

Ferrara et al teach a method for treating trauma affecting the vascular endothelium (e.g., injuries to the blood vessels or heart as well as the vascular network of organs, wounds, incisions and ulcers) comprising administering to an animal or human suffering from said trauma a pharmaceutical composition comprising an effective amount of recombinant VEGF (see at least Summary of the Invention; particularly col. 3, line 65 continues to line 19 of col. 4; col. 6, lines 1-12; col. 14, lines 19-34). Ferrara et al. also disclosed that "VEGF" includes VEGF analogues, variants and fragments having the biological activity of corresponding native VEGF (col. 5, lines 24-68; col. 6, line 13 continues to line 45 of col. 10). Ferrara et al. further defined a therapeutically effective amount of VEGF as an amount that is effective to prevent, lessen the worsening of, alleviate the treated condition and in particular the amount is sufficient to enhance the growth of vascular endothelium *in vivo* (col. 14, lines 35-46). The therapeutically effective dosage is greater than about 0.1 ng/cc to a maximum dose that is efficacous but not unduly toxic (col. 16, lines 47-56). Ferrara et al. further teach that VEGF can be combined with other novel or conventional therapies (e.g., growth factors such as aFGF, bFGF, PDGF, IGF, NGF, EGF, TGF-alpha) for enhancing the activity of any of the growth factors including VEGF, in promoting cell proliferation and repair (col. 16, lines 57-68). Ferrara et al. do not teach the use of both VEGF and GM-CSF in a method for inducing formation of new blood vessels.

Bussolino et al. teach that (p. 835, sentence bridging col. 1-2), "Subnanomolar concentrations of GM-CSF and G-CSF induce the proliferation of endothelial cells derived from human vessels…." The optimal dose for proliferation was about 10 ng/ml (p. 835, col. 2, lines 6-8). They also state (p. 835, col. 2, first full paragraph), "The primary effect of GM-CSF and G-

CSF on vasculature *in vivo* is the stimulation of the angiogenesis process…. GM-CSF also induces angiogenesis in rat connective tissues probably by a direct effect on endothelial cells and by a recruitment of activation of macrophages which release angiogenetic factors." It is noted by the authors that (p. 836, col. 2, second full paragraph), "...*in vivo* bone marrow endothelial cells proliferate in subjects treated with GM-CSF."

Orazi et al. teach administration of GM-CSF by infusion to patients who had received high-dose cyclophosphamide cancer chemotherapy. It was found (p. 2615, last paragraph) that after GM-CSF treatment, "the BM [bone marrow] vascular network was much increased and showed branching, tortuosity, and dilation. The proportion of endothelial cells of BM arterioles, capillaries, and sinusoids expressing CD34 was also significantly increased (Table 5)…."

It would have been obvious at the time the invention was made to the artisan of ordinary skill to modify the method of Ferrara et al. by utilizing GM-CSF as an additional angiogenic factors, and optionally (as taught by Ferrara et al.) aFGF, EGF or PDGF as a further angiogenic protein. The methods taught are for repair of tissue damaged by, for example, ischemia in a patient through angiogenesis. As disclosed by Ferrara et al. the tissue damaged may be coronary tissue. In combination, each compound: VEGF and GM-CSF, would have functioned as it did separately, such that the results of the combination were predictable. That is, since each compound was known to promote new blood vessel formation *in vivo*, the combination would have also been expected to do that as *per* the methods of Ferrara et al. Because Ferrara et al. taught administration of VEGF for prevention or treatment of a condition by promoting growth of vascular endothelium *in vivo* and because both GM-CSF and VEGF were shown to have that property, it would have been obvious to administer one or both of the angiogenic compounds prior to a condition involving blood vessel damage or administer after the damage if the condition could not have been anticipated. It would have been routine optimization to have determined the preferred time of pretreatment or treatment relative to onset of the condition. Furthermore, the advantage of utilizing combinations of angiogenic factors is the attainment of at least the additional effects of administered angiogenic factors. An ordinary skilled artisan would have had a reasonable expectation of success in light of the teachings of Ferrara et al., Bussolino et al. and Orazi et al.

While Ferrara et al., Orazi et al. and Boussolino et al. are silent with respect to the amount of increase in vessel length, diameter or performance in standard hindlimb ischemia or cornea micropocket assay and EPC incorporation into foci, the dosages of Ferrara et al. and reported results of Boussolino et al. and Orazi et al. are consistent with the required levels of activity in the instant claims.

Applicants' arguments that still pertain to the new rejection above are addressed here:

Applicants argue in paragraph 2 of page 7 of the response that "the Examiner must establish that there is some motivation in one or the other of the cited references or in the state of the art at the time the invention was made to combine the references…." The argument has been fully considered, but is not persuasive. According to *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396 (2007), applying prior art elements according to known methods to yield predictable results is sufficient to establish motivation. In this case, both VEGF and GM-CSF were taught as useful *in vivo* for angiogenesis. Ferrara et al. taught treatment of conditions, such as coronary ischemia, with one or more compounds that promote angiogenesis. Applicants argue, p. 7, ¶ 5, that "the deficiency of either Kaplan or Ferrara is that neither reference teaches or suggests GM-CSF and/or G-CSF. The argument has been fully considered, but is not persuasive. Because neither patent teaches using GM-CSF, this rejection is not anticipatory but is set forth under 35 USC 103.

Applicants argue on pages 9-10 that Bussolino (1991) supports unpredictability of using GM-SCF and bFGF, thereby not providing a reasonable expectation of success with this combination. The argument has been fully considered, but is not persuasive. Even though Bussolino, 1991, is no longer replied upon, it is important to note that the effects of the combination of GM-CSF and bFGF are not pertinent to the instant claims or rejection. Claim 70 does not name bFGF but aFGF as an additional angiogenic protein. The use of aFGF is supported by Ferrara et al. with VEGF. Bussolino, 1994, and Orazi et al. (1992) do support the use of GM-CSF *in vivo* for angiogenesis, which would have been conducive to use with VEGF or other angiogenic factor(s).

Applicants argue in the last paragraph of page 10 that "none of the references teaches or suggests the predictability of the combination of VEGF and GM-CSF for increasing

angiogenesis in vivo…." The argument has been fully considered, but is not persuasive. Because as taught by the prior art relied upon that both VEGF and GM-CSF function *in vivo* to increase angiogenesis with new blood vessel formation, one of ordinary skill in the art would have reasonably expected the combination of VEGF and GM-CSF to promote angiogenesis and be useful in the treatment of ischemia.

Prior Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Bkifalvi et al. (Leukemia, 8(3): 523-529) discusses the angiogenic properties of GM-CSF, citing the work of Bussolin (1991) and Rubbi-Brandt (see immediately below) among others. Both *in vivo* and *in vitro* studies are cited which support the ability of GM-CSF to promote new blood vessel formation (p. 526, last paragraph of col. 2).

Rubbia-Brandt et al. (Virchows Archiv B Cell Pathol. 60:73-82, 1991) used an implanted pump in rats to observe the effects of GM-CSF on surrounding tissue. They report (p. 78, sentence bridging col. 1-2), "With GM-CSF, intense proliferation of fibroblastic cells and newly formed blood vessels predominated, especially at the internal portion of the capsule...."

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire Kaufman, whose telephone number is (571) 272-0873. Dr. Kaufman can generally be reached Monday, Tuesday, Thursday and Friday from 9:30AM to 2:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached at (571) 272-0835.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Official papers filed by fax should be directed to (571) 273-8300. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to

avoid the processing of duplicate papers in the Office.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Claire Kaufman, Ph.D.
/Claire Kaufman/
Patent Examiner, Art Unit 1646
February 23, 2009